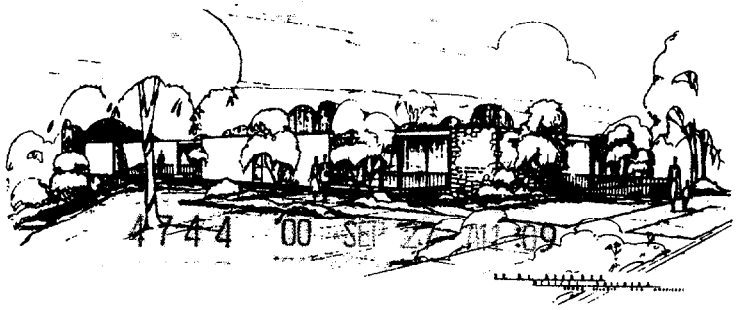
INTERNAL MEDICINE
AND
ALLERGY



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September 15, 2000

Dockets Management Branch
Division of Communications Management
HFA-305 Food & Drug Administration
5600 Fishers Lane - Rm. 1061
Rockville, MD 20857

Dear Sir/Madam:

This letter is in response to Guidance Document, Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products, draft guidance document distributed for comment purposes only. I am submitting my comments and suggestions regard this draft document accordingly. The draft I have is 17 pages.

In differentiating the two conditions, seasonal allergic rhinitis and perennial allergic rhinitis, we have to keep in mind that seasonal is a relatively acute condition that usually lasts for only a few weeks in contrast to perennial allergic rhinitis which is a chronic condition. One involves stress and acute adaptation syndrome and the other involves stress and the chronic adaptation syndrome, each of which have different metabolic consequences, even though the end organ manifestations may seem to be similar. The psychologic adjustments are different and require appropriate consideration. Whenever we treat a patient, we not only must treat the symptoms but also the emotional adjustment reaction which largely involves the art of medicine.

Overall, treatment directed at perennial allergic rhinitis should be different from that for seasonal allergic rhinitis, as well as vasomotor rhinitis, which is frequently a component of perennial allergic rhinitis. We are using topical corticosteroids to treat perennial allergic rhinitis to the extent that we are neglecting other modalities of treatment that are more valuable in the long term picture. There is no doubt that steroids contribute on a short-term basis to improving quality of life, but how much they contribute on a long-term basis has not been truly adequately evaluated. A one-year study is of little value in a condition that goes on for many years. We are treating the nasal and eye symptoms

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but not treating the whole patient. Clinical trials must take into consideration anxiety, depression, and quality of life with appropriate questionnaires for each. The associated anxiety and reactive depression is not simple to evaluate from the standpoint that it is sometimes the cart and sometimes the horse. This is extremely important as it applies to the patients who have chronic perennial symptoms. In many of them, the symptoms have been recurrent since early childhood and in such cases there has also been depression since early childhood, frequently antedating the onset of the respiratory symptoms. Thus, when we look at the natural history of disease we have to be able to interpret what we are accomplishing with treatment. I have had patients who have had complete relief of their perennial nasal symptoms with medication directed at such symptoms, only to find that the patients will commit suicide later on on account of interference of the frustrated cry that has been suppressed by the medications. Many patients need their nasal symptoms. Many patients are being overtreated for their symptoms in which they should only have partial relief instead of complete relief.

Today, treatment seems to be directed at giving high doses of medications once or twice a day to suppress symptoms as much as completely possible. Symptoms should be treated to the point that the patient is not too uncomfortable but should be allowed to have a certain amount of emotional exit through the respiratory tract.

This in turn leads to the problem of determining how to monitor for adverse effects. We would reduce the risk of adverse effects by reducing the amount of medication used in treatment and ultimately lead to a more happy, well adjusted patient once he or she realizes what is the range of normal symptoms to be differentiated from what is abnormal. Neither seasonal allergic rhinitis nor perennial allergic rhinitis is a truly abnormal condition except when symptoms are excessive. The problem is defining what is excessive.

Naturally we want to control symptoms to the point that we do not get complicating sinusitis, otitis media and lung disorders. The upper respiratory tract does have a role in influencing the reaction in the lower respiratory tract, as we are all aware. With proper treatment of the upper respiratory tract we help protect against certain difficulties in the lower respiratory tract. When we overtreat the upper respiratory tract with nasal steroids and/or antihistamines, we frequently get a cough and increase in chest symptoms. At such time we should cut back on dosage. Instead, doctors frequently prescribe various cough medications, antibiotics and other measures to try to help overcome the symptoms in the lower respiratory tract rather than simply reducing medication

prescribed for upper respiratory symptoms. Thus, in monitoring patients for treatment of upper respiratory symptoms it is also important to observe whether or not cough and/or other lower respiratory symptoms develop while the patient is under treatment. Such symptoms will frequently be mistaken as a respiratory infection, etc., rather than over treatment.

About 50 years ago, Dr. Hans Selye outlined the emotional and metabolic changes that take place in relation to acute stress and also in relation to chronic stress in the general adaptation syndrome. Protocols should incorporate his suggestions from the emotional and physiologic metabolic reactions that take place accordingly in seasonal versus perennial allergic rhinitis. True vasomotor rhinitis is a neglected disorder on the basis that it is seemingly relatively uncommon. Part of the reason that it is seemingly relatively uncommon is related to the fact that such patients do not end up under the care of the allergist on account of the allergy tests being negative. Such patients are commonly neglected and simply have to live with their condition on the basis that we don't take it seriously. The serious problem in such patients is the underlying psychiatric disturbance and emotional adjustment.

Too much emphasis is being placed today in the treatment of end organ responses and not enough attention to the central nervous system, endocrine, metabolic, and other factors that play a role in the peripheral manifestations. Patients life styles are extremely important.

At the bottom of Page 5, you go into corticosteroid issues which is our main concern. I published a book "Corticosteroids in Medical Practice" with over 3,000 references nearly 40 years ago. I have always maintained my interest in the corticosteroids. When systemic corticosteroids are involved, it is almost always prednisone that is the standard of therapy. Even though there are certain theoretical advantages to prednisolone, there are definite advantages to hydrocortisone which is the natural corticosteroid that often gives relief of symptoms in small dosage that is most effective both centrally and peripherally. It is nice to have a steroid, such as hydrocortisone, that gives the patient forewarning of excess dosage, such as fluid retention and/or elevation of blood pressure, or other side effects, so that emphasis can be placed on measures that will help reduce steroid need. It is also of interest that patients who are on prednisone and getting side effects do better when they are switched to hydrocortisone in a lower dosage than the accepted 4:1 ratio milligram per milligram basis for potency. Thus, when we resort to systemic corticosteroids today we are not

adequately using hydrocortisone properly and overemphasizing the use of prednisone. We can change from hydrocortisone to prednisone if there is fluid retention and increased blood pressure.

It is also unfortunate that ACTH is now only used for diagnostic purposes and not for treatment on the basis of risk of allergic reactions to ACTH, even though we have much more purified preparations of ACTH now than in the past. There are few patients today receiving corticosteroids who are still allergic to ACTH from the previous use of the old crude ACTH. The potential value of ACTH is borne out in my book. I also previously wrote an article "ACTH - Useful in Therapy?" which went into the pros and cons of ACTH therapy. Now that there are so few patients left who are allergic to ACTH this is a good time to use pure forms of ACTH in treatment. We now also have corticotropin releasing factor and other factors from the pituitary gland to help us, including factors that affect parathyroid hormone production and other hormones. We all appreciate the value of estrogens in helping prevent and control osteoporosis in women receiving corticosteroids, inhaled or systemic, and possibly the value of anabolic steroids in men. The possible role of anabolic hormones is not fully appreciated.

On the bottom of Page 5 you start to address assessment of adrenal function using either timed urinary free cortisol level measurement and/or plasma cortisol AUC levels pretreatment vs after at least six weeks post treatment with study medication. I certainly agree with the use of placebo and not on an active control like prednisone in these studies on the basis that the systemic equivalence of the prednisone and inhaled medication are not the same. It is only with the placebo control that comparison of adrenal suppression may be made. In addition, it must be kept in mind that assessment of adrenal function using urinary and plasma cortisol levels is still relatively crude. It is still controversial how much the free cortisol reflects the true active hydrocortisone out of the total amount of hydrocortisone and other corticosteroids that may be present. Endocrinologists have been fighting this battle for over 30 years in differentiating active free cortisol from protein bound, from conversion and turnover ratios, responsiveness of receptors and other factors, particularly bioavailability. My main point is our tests remain very crude.

In relation to evaluation of possible cataract formation by slit lamp exam pre and post treatment, such exams should be done on patients at least once a year regardless of who much corticosteroid they receive by inhalation and/or systemically. Obviously, this is important in the patients on nasal steroids. Annual exams also must

include eye pressure measurement. This is on the basis that the circulation from the nose is such that nasal corticosteroids may pass into the circulation of the eyes.

On Page 6 you address oral formulations and bioequivalence between oral formulations. This is much more difficult to measure than outlined in the paragraph on Page 6. This also applies to topical nasal formulations as outlined in the next paragraph. The comparability approach has more difficulties.

Page 7 addresses the issue of safety monitoring which is extremely difficult on account of the multiplicity of factors involved and which issues are most important. The lab tests are crude tests but worthwhile. Normal findings are helpful, but we should not be complacent in addressing changes that are in the normal range.

Again, on Page 8 in relation to corticosteroid issues, the tests are totally inadequate. There has been too much of a trend to use the corticosteroids in young children, thinking that the inhaled steroids are relatively safe. Even though the infection rate may seem to be lower in children on inhaled corticosteroids and Cromolyn-like drugs, when such children do get an infection it is frequently harder to treat than previous infections they had before being placed on steroids.

I do not know about the anticholinergics. It is very important for parents to be aware of this fact when they sign patient consent forms for drug studies. Even though innumerable studies have been completed comparing active drug with placebo, it is truly remarkable how little is known about the natural history of each disorder in the nonsteroid treated children. The possible beneficial effect of corticosteroids on remodeling has been far overemphasized and it is still unproven. Again, the controls are unsatisfactory. Any new drug approved on the market should be on condition that the double blind placebo controlled studies are continued long enough to determine whether or not there are significant long-term unfavorable effects that help confirm it should be withdrawn from the market. We need conditional approvals of drugs that are released for sale to allow further study without protracted delay in release to the market place.

When two active drugs are compared they usually come out equal in effectiveness. It is hard to design a study that differentiates one from the other. However, when a placebo is inserted it helps bring out differences between the two active drugs as well, better than a study that does not include a placebo. It seems that everyone participating in the study is more alert to look for differences,

both subjectively and objectively. Thus, there should always be an arm in the study that contains the placebo, not necessarily in equal number in the others.

In summary, my main concern is the extent to which corticosteroids have been accepted as first line of defense in allergic disorders. The risk of growth suppression is small but sufficient that I am happy that the FDA brought this out in requiring such labeling. The corticosteroids have a broad spectrum of action on metabolic processes. Thus, it is not surprising that they may affect growth, but we must keep in mind that they have a broad spectrum effect, and, in turn, broad spectrum of side effects.

Tests measuring adrenal cortical function are inadequate. More sensitive tests are appropriate, such as using 1/100th of the dose of ACTH used currently in measuring adrenal responsiveness and reserve. The old fashioned insulin tolerance test is good. The glucose tolerance test also has merit. Reactive hypoglycemia is a real problem in patients who have had corticosteroids. ACTH studies that include DHEA may be helpful. Studies that include measurement of anabolic hormones is important, such as keto-steroids. We need a proper measurement of both catabolic and anabolic balance. We have to consider the effect on salt and water retaining hormones, including Aldactone. Changes in eosinophil counts in patients receiving corticosteroids, both during cortico-steroid therapy and after corticosteroid withdrawal are important. Patients may have subjective improvement while on corticosteroids only to find that their eosinophil levels rise rather than fall, indicating that treatment has been primarily on a subjective basis rather than objective. Naturally we are concerned about the effects on lipids. Blood testing should always include lipid panels, fasting.

It is truly remarkable how little nasal corticosteroid is needed to help control upper respiratory symptoms. Thus, emphasis should not be placed on the use of powerful nasal steroids in patients who do not need them. Nasonex by Schering appears to be a step in the right direction and in turn as been associated with less risks. However, this does not mean it will not cause growth suppression in dosage comparable to that used with the more potent nasal steroids and/or which patients will react to small doses with adverse effects. The sensitivity to corticosteoids varies significantly both in terms of effectiveness and side effects.

Our search must constantly be for medications that are more specific in action and associated with less side effects, such as the leukotriene antagonists and other products in development. They should be approved on all insurance plans for treatment of patients

before having to resort to nasal steroids or inhaled asthmatic steroids. More effort and interest must be taken in taking measures that will help reduce the need for steroids and also help reduce side effects when they are employed, such as adding estrogens in perimenopausal and postmenopausal women, testosterone and/or other anabolic hormones in men in comparable metabolic periods of life.

Low cholesterol diets are important and medications that help control lipids. We have to be more careful about controlling blood sugar to make sure we do not cause hypoglycemia. Electrolyte balance, serum and urine osmolality and other metabolic changes need more consideration. We have become too complacent about how we use corticosteroids since the drug companies have made the inhaled steroids appear so safe. The FDA is our only hope to keep the practicing physician on the right track.

Again, I want to emphasize the innumerable subtle changes in metabolic and endocrine balance, neural hormonal balance, cerebrocortical, and feedback mechanisms that take place with corticosteroid therapy in a patient with acute stress, such as seasonal allergic rhinitis versus the patient under chronic stress, such as with perennial allergic vasomotor rhinitis, and other disorders depending on for which one the patient is receiving for treatment.

Thank you for your consideration.

Very sincerely yours,

Milan L. Brandon, M.D.

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MLB/bdm

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